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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/655,272	Applicant(s) HONORE ET AL.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *1-30 and 39-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-51* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group IV, claims 31-38, drawn to a method of screening substances capable of modulating the activity of the purified protein in Paper No. 11 (26 March 2002) is acknowledged.

Claims 1-30 and 39-51 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11 (26 March 2002).

Claims 31-38 are under consideration in the instant application.

Priority

1. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France on 05 March 1998. It is noted, however, that applicant has not filed a certified copy of the FR98/02725 application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

2. The information disclosure statement filed 05 September 2000 (Paper No. 4) fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language (specifically, FR 2744730). It has been placed in the application file, but the information referred to therein has not been considered.

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

4. The abstract of the disclosure is objected to because the legal term "said" is used. Applicant is reminded of the proper language and format for an abstract of the disclosure. Correction is required. See MPEP § 608.01(b). Correction is required. See MPEP § 608.01(b).

5. The disclosure is objected to because of the following informalities:

5a. The Brief Description of Drawings for Figure 2 refers to four amino acid sequences, but disclosed sequences are not accompanied by the required reference to the relevant sequence identifiers.

5b. The Brief Description of Drawings for Figure 4 refers to a part (f). However, there is no Figure 4(f).

5c. The Brief Description of Drawings for Figure 5 does not refer to Figures 5(a) and 5(b).

5d. The Brief Description of Drawings for Figure 6 does not refer to Figures 6(b)-6(i). Additionally, there is no Figure 6(a).

5e. The Brief Description of Drawings for Figure 8 does not refer to Figures 8(a)-8(f).

5f. The Brief Description of Drawings for Figure 9 does not refer to Figures 9(a)-9(e). Please also note that pg 13, line 11 of the specification refers to Figure 9(f). However, no such Figure is present in the instant application.

5g. The Brief Description of Drawings for Figure 10 does not refer to Figures 10(a)-10(b).

5h. At pg 6-7, the specification refers to TREK-1 as having the amino acid sequence of SEQ ID NO: 2. However, the paper copy of the sequence listing has the amino acid sequence of SEQ ID NO: 2 as being TRAAK (which matches the amino acid sequence of TRAAK in Figures 1-2 and SEQ ID NO: 1). According to the paper copy of the sequences, the amino acid sequence of TREK-1 is SEQ ID NO: 4 (which matches the amino acid sequence of TREK in Figure 2) and not SEQ ID NO: 2. Please also note that at pg 7, lines 12-13, SEQ ID NO: 2 is an amino acid sequence and not a nucleic acid sequence.

5i. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD FOR SCREENING SUBSTANCES CAPABLE OF MODULATING THE ACTIVITY OF A TRAAK POTASSIUM CHANNEL". Appropriate correction is required.

Claim Objections

6. Claims 31-38 are objected to because of the following informalities:

6a. Claims 31-38 depend from claims 1-3 and 19-24, which are currently withdrawn.

6b. Claims 31-38 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim (i) should refer to other claims in the alternative only and (ii) cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 31-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening substances capable of modulating the activation of a purified mechanosensitive potassium channel having the amino acid sequence set forth in SEQ ID NO: 2 or 4, which comprises: (a) transferring the purified nucleic acid sequence that encodes the channel consisting of the amino acid sequence of SEQ ID NO: 2 or 4 into a cellular host; (b) culturing said host under suitable conditions for expression of said channel; (c) bringing into contact the substance to be screened with said host expressing said channel; and (d) measuring the potassium current of said channel, wherein an increase or decrease in potassium current indicates modulation of activation of said channel, does not reasonably provide enablement for a method for screening substances capable of modulating the activity of the purified protein which comprises: (a) reacting varying amounts of the substance to be screened with a cellular host; and (b) measuring the effect of the substance to be screened on a potassium channel expressed by the cellular host. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification of the instant application discloses that the TREK-1 channel (SEQ ID NO: 4) and the TRAAK channel (SEQ ID NO: 2) is activated by tension applied to a cell membrane or by the application of polyunsaturated fatty acids, such as arachidonic acid (pg 15-19; Figures 6-9). The specification teaches that activation of the TRAAK channel is reversible and dependent on the concentration of the polyunsaturated fatty acid applied (pg 18, lines 2-4; Figure 9). The specification also teaches that riluzole, a neuroprotective agent, activates the

TREK-1 and TRAAK channels (pg 19, lines 8-11; Figure 10). However, the specification does not teach screening for substances capable of modulation of potassium channel activation using any potassium channels other than TREK-1 (SEQ ID NO: 4) and TRAAK (SEQ ID NO: 2). Relevant literature reports that that potassium channels constitute the most diverse class of ion channels with respect to kinetic properties, regulation, pharmacology, and structure (pg 1329, col 2; Lehmann-Horn et a. Physiol Rev 79 (4): 1317-1372). Additionally, over 50 distinct channels have been identified in humans in both excitable and non-excitable cell types. The channels are involved in the control of a variety of cellular functions, including neuronal firing, cellular proliferation, and neurotransmitter and hormone secretion (pg 7887, ¶ 1; Chavez et al. J Biol Chem 274(12): 7887-7892, 1999). Undue experimentation would be required of the skilled artisan to screen all possible mechanosensitive potassium channels and their derivatives with all possible substances. The skilled artisan would not be able to predict the result of incubating a substance with any potassium channel derivative because certain positions in an amino acid sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the potassium channels which are tolerant to change (e.g. such as by amino acid substitutions

or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and to screen all possible mechanosensitive potassium channels and their derivatives with all possible substances, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any limitations as to the protein to be screened, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 31-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 31-38 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating how the effect or activity measured has to change in order to identify a substance. Would there be an increase in activity? A decrease? Does the result depend upon the type of substance administered?

10. The term "varying amounts" in claims 31-38 is a relative term which renders the claims indefinite. The term "varying amounts" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, it is not clear if the term "varying amounts" encompasses one specific amount of a substance or a range of amounts. Also, the upper and lower limits of the quantity of substance administered cannot be determined.

11. The term "activity" in claims 31-38 is a relative term which renders the claims indefinite. The term " activity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what activity is being modulated. For example, does the term "activity" mean binding? Proliferation? Differentiation? Potassium currents?

12. The term "effect" in claims 31-38 is a relative term which renders the claims indefinite. The term "effect" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably

apprised of the scope of the invention. It is not clear what effect is being measured. Binding? Proliferation? Differentiation? Potassium currents?

13. Claims 31-38 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: (a) transferring the purified nucleic acid sequence that encodes the channel consisting of the amino acid sequence of SEQ ID NO: 2 or 4 into a cellular host and (b) culturing said host under suitable conditions for expression of the potassium channel having the amino acid sequence of SEQ ID NO: 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 31-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gubitosi-Klug et al. (J Biol Chem 270(7): 2885-2888, 1995) in view of Fink et al. (EMBO J 15(24) : 6854-6862, 1996).

Gubitosi-Klug et al. teach a method of screening substances capable of modulating the activity of the human brain delayed rectifier potassium channel, Kv1.1. Gubitosi-Klug et al. teach transforming *Spodoptera frugiperda* (Sf9) cells with a Kv1.1 virus (pg 2885, col 2, ¶ 3). Gubitosi-Klug et al. also disclose incubating the Sf9 cells expressing Kv1.1 with arachidonic acid, docosahexaenoic acid, 5-HETE, eicosa-5,8,11-trienoic acid, eicosa-8,11,14-trienoic acid, and methyl ester of arachidonic acid (abstract; pg 2885-2886, col 2, ¶ 5; Figures 1-2). The current recording of Kv1.1 is measured after the administration of each substance. Gubitosi-Klug et al. teach that incubation of Sf9 cells with arachidonic acid results in an increase in rate of channel activation (abstract, pg 2886, col 1, Figure 1).

Gubitosi-Klug et al. does not teach transforming Sf9 cells with DNA for a mechanosensitive potassium channel.

Fink et al. teach the structural and functional properties of TREK-1, a mammalian TWIK-1 related potassium channel (SEQ ID NO: 4 of the instant application).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Gubitosi-Klug et al. for a method of screening substances capable of modulating the activity of Kv1.1 by utilizing the potassium channel, TREK-1, as taught by Fink et al. The person of ordinary skill in the art would have been motivated to make that modification because evidence indicates that the TREK-1 channel is activated by extracellular potassium in a controlled external sodium concentration and such a

sensitivity to external potassium could have an importance in pathologies where large variations in external potassium occur, such as epilepsy and brain or heart ischemia. The person of ordinary skill in the art would have expected success because similar substance screening assays utilizing other ion channels were being performed at the time the invention was made. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Maingret et al. J Biol Chem 274(3): 1381-1387, 1999.

Maingret et al. J Biol chem 275(14) : 10128-10133, 2000.

Patel et al. Nature Neurosci. 2(5) : 422-426, 1999.

Reyes et al. J Biol Chem 273(47): 30863-30869, 1998.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

BEB
Art Unit 1647
June 12, 2002